PATENT COOPERATION TREATY

4 MAR 2005

RECD 04 NOV 2004

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
14729WO16632		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL 03/00728	04.09.2003	04.09.2002
International Patent Classification (IPC) or both national classification and IPC		
A61L27/38		
Applicant		
YISSUM RESEARCH DEVELOPMENT COMPANY OF THE ...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31.03.2004	03.11.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ganschow, S Telephone No. +49 89 2399-7807

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL 03/00728

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-70 as originally filed

Claims, Numbers

1-50 as originally filed

Claims, Pages

71-80 as originally filed

Drawings, Sheets

1/11-11/11 as originally filed

Drawings, Figures

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 38-45

because:

☒ the said international application, or the said claims Nos. 38-45 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	49-50
	No:	Claims	1-48
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-50

Industrial applicability (IA)	Yes:	Claims	1-37, 46-50
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 38-45 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Documents

1.1. The present application relates to a bone forming composition comprising bone marrow cells, demineralized bone matrix and a site-responsive polymer.

1.2. Reference is made to the following documents cited in the International Search Report:

D1: US 6 437 018 B1 (GERTZMAN ARTHUR A ET AL) 20 August 2002 (2002-08-20)

D2: US 6 326 018 B1 (GERTZMAN ARTHUR A ET AL) 4 December 2001 (2001-12-04)

D3: EP 0 419 275 A (OSTEOTECH INC) 27 March 1991 (1991-03-27)

D4: US 5 314 476 A (PREWETT ANNAMARIE B ET AL) 24 May 1994 (1994-05-24)

D5: WO 96 28539 A (MORPHOGEN PHARMACEUTICALS INC ;NORTH SHORE UNIV HOSPITAL (US)) 19 September 1996 (1996-09-19)

D6: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; April 1995 (1995-04) CONNOLLY J F: "Injectable bone marrow preparations to stimulate osteogenic repair." Database accession no. NLM7641502 XP002228844

D7: WO 99 11298 A (GENSCI REGENERATION LAB INC) 11 March 1999 (1999-03-11)

D8: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; November 1982 (1982-11) LINDHOLM T S ET AL: "Extraskeletal and intraskeletal new bone formation induced by demineralized bone matrix combined with bone marrow cells." Database accession no. NLM6216033 XP002228845

1.3. Reference is made to the passages cited in the International Search Report.

2. Clarity

2.1. Present claim 1 relates to 'site-responsive polymers'. However, dependent claim 26 presenting a group of various possible compounds refers to oligomers, glycerol, drugs in general, hormones, enzymes and peptides which do **not** appear to fall into the scope of the term 'site-responsive **polymer**'.
This inconsistency leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

3. Method of treatment

3.1. For the assessment of the present claims 38-45 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Novelty

4.1. Document D1 discloses demineralized bone particles mixed in a fluid carrier such as sodium hyaluronate (=site-responisve polymeric system). Bone marrow cells may be added (see claim 26). D1 also teaches a method of introducing the composition into bone.

4.2. D2 teaches a malleable bone putty and a flowable gel composition for application to a bone defect site to promote new bone growth. The composition comprises demineralized bone powder and hyaluronic acid and chitosan (see claim 1). Bone marrow cells or mesenchymal stem cells may also be included (column 6, line 17).

4.3. D3 discloses a flowable demineralized bone powder composition and its use in bone repair. The composition comprises a biocompatible carrier such as glycerol, polyvinyl alcohol, cellulosic esters, gelatin, collagen, polyacrylic acid salts or oligosaccharide (column 5, line 25-38 and claims 1-3). It may also contain mesenchymal stem cells (claim 18).

4.4. Document D4 relates to a flowable osteogenic composition comprising demineralized bone particles, a biocompatible fluid carrier (*e.g.*, oligosaccharides, polysaccharides, glycerol, alginic acid) and optionally bone marrow cells/ mesenchymal stem cells.

4.5. Thus, D1-D4 already disclose bone forming combinations comprising bone marrow cells, demineralized bone matrix and a site-responsive polymer.

Present claims 1-48 referring to a composition for use in bone replacement are therefore not novel in terms of Art. 33(2) PCT.

5. Inventive step

5.1. Since claims 1-48 are not novel pursuant to Art. 33(2) PCT, no final decision can be made concerning inventive step. However, if novelty could be established, the present application would probably not fulfill the criteria of Art. 33(3) PCT for the following reasons:

5.2. Present documents D5 and D7 already relate to bone forming compositions comprising a) site-responsive polymers in combination with b) bone marrow cells and demineralized bone, respectively.

5.3. D6 discloses that injections or direct transplantation of bone marrow preparations stimulates osteogenesis. Addition of demineralized bone matrix increases the efficiency of bone marrow to form bone.

D8 discloses that combinations of bone marrow demineralized bone matrix act synergistically to induce extraskeletal and intraskeletal new bone formation.

5.4. Thus, it would have been obvious to the person skilled in the art to add either bone marrow cells or demineralized bone to the compositions according to D5 and D7, thereby arriving at a composition as claimed in present claim 1.

The subject-matter of claim 1 does therefore not involve an inventive step (Article 33(3) PCT).

5.5. Moreover, nothing inventive (Art. 33(3) PCT) can be seen in a kit according to present claims 49-50 comprising standard features.

However, it is noted that the kit according to present claims 49-50 **does not comprise bone marrow cells** resulting in a lack of clarity as independent claim 49 does not contain all features essential to the definition of the invention. Hence, claim 49 does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.